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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/774,843	PELED ET AL.	
	Examiner	Art Unit	
	MARIA LEAVITT	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *401,411,414,416,419,422-424,437,438,464,465,469-471 and 478-480* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-471 and 478-480* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07-01-2009;06-29-2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 06-10-2009 has been entered.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.
2. Claims 401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-470, 471 and 478-480 are pending. Claims 401 and 411 have been amended and claims 412, 417, 466, 467, 472-477 and 481 have been cancelled by Applicants' amendment filed on 06-10-2009.
3. Applicants' election of the following species: colony-stimulating factor (SCF) as a single species of cytokine and "benzamide" as the species of nicotinamide analog in Applicants' response filed on November 14, 2006 was previously acknowledged.
4. Therefore, claims 401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-471 and 478-480 are currently under examination to which the following grounds of rejection are applicable.

Priority

This application which claims the benefit under 35 U.S.C. 119(e) of prior-filed provisional application 60/404,137, filing date 08/19/2002, and 60/376,183, filing date 04/30/2002, is acknowledged.

Review of the priority documents provides no literal or figurative support for the claimed invention of "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide". Therefore, the priority date for the claimed limitation "culturing said cells in the presence of 1.0 mM to 10 mM of exogenously added nicotinamide' is found in the disclosure of the instant U.S. Application filed on 02-09-2004.

Rejections maintained in response to Applicants' arguments or amendments.

Claim Rejections - 35 USC § 103

Claims 401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-471 and 478-480 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002).

Brown R. teaches a method for *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- cells derived from umbilical cord blood (p. 1, [0010]). Brown R. discloses the presence of appropriate growth factors in the medium such as interleukins, CSF, stem cell factor, thrombopoietin (TPO), interleukin-1 (IL-I) and interleukin-6 (IL-6) which influence the rate of proliferation and the distribution of cell types in the population (p. [0049]) (**Current claim 401, subpart (a) in part**). Moreover, Brown R. discusses that one or more of the cytokines playing a role for driving proliferation in hematopoietic cells can be added to the culture medium at

different stages of the culture to alter the cell population including FLT3, STF, IL-I, IL-6, TPO, etc. (p. [0050]) and cytokines such as, granulocyte colony-stimulating factor (G-CSF), and granulocyte-macrophage colony stimulating factor GM-CSF) (p. 4, [0049]). Note that G-CSF is a late acting cytokine. Additionally, human serum albumin (HSA) is used to provide a source of protein in the culture media (p. 5,[0054]) (**Current claims 422, 423 and 424).** Moreover, Brown R teaches the components of the basal medium for expansion of CD34+/CD38- cells *ex vivo* including nicotinamide at concentration of 4 mg/L (p. 3, col. 2, [0040] and p. 4, table I) (4 mg/L is equivalent to 0.033mM). Brown discloses that Iscove's modified Dulbecco's medium (IMDM) can reformulated and "it is expected that the reformulation will contain those essential components of IMDM in amounts 0.1 to 10, preferably 0.5 to 2 times, most preferably 0.8 to 1.2 times their amounts" (p. 4, [0045]). That is nicotinamide at concentrations of 40 mg/L (e.g., equivalent to 0.330mM). Furthermore, Brown discloses that if the media is being used to maintain or enrich the amount of CD34+/CD38- cells in a cell population, it is preferable that growth factors which accelerate differentiation of CD34+/CD38- cells to CD34+/CD38+ cells be avoided (p.6, [0068]). **(Current claims 401, 414, 416, 422-424).** Furthermore, Brown discloses that "Early progenitors (CD34, CD38, HLA-DR), myeloid markers (CD33, CD14, CD45), lymphocyte markers (CD3, CD7, CDI9), red blood cell markers (glycophorin A) and megakaryocyte/platelet determinants (CD41a)" and assesses by FACS the cluster of markers CD45, CD14, CD34, CD20, CD33, CD3, CD7, CD56, CDIO, CD4, CD8 (BDIS) and glycophorin A (p. 8, [0102]), Thus Brown does not explicitly discloses diminished expression of CD33, CD14, CD3 and other surface makers, reduction of said markers is inherently anticipated in an expanded population of CD34+ cells as CD33, CD14, CD3 makers identify differentiated

stem cell populations (**Current claim 419**). Furthermore, Brown R. exemplifies cultures of the bone marrow CD34+ enriched population showing CD34+/CD38- cells with significant expansion at day 3, 7 and 14, in the absence and presence of serum and low concentrations of IL-3, IL-6 and SCF (p. 10, [0119]) reading on expansion of cells for a period of up to three weeks (**Current claims 419, 464 and 465**)

Brown does not specifically teach concentrations of exogenously added nicotinamide of 1.0 mM to 10 mM.

However, at the time the invention was made, Block discloses a chemically defined mammalian cell culture medium that supports maintenance and long term clonal growth of mammalian hepatocytes and other cells (col. 1, lines 10-15, col. 2, lines 1-3; col. 7, lines 1-5). The stock basal media contains albumin and other serum components (col. 14, line 19; Table IV). Block teaches various growth factors can be added to the stock basal media to induce accelerated growth (col. 11, lines 28-38) including concentrations of nicotinamide in the range of 1-3050 mg/L, **preferably 610.0 mg/L** (610-3050 mg/L is equivalent to 5 to 25 mM of nicotinamide), see Table II; col. 10, lines 30-50. Furthermore, Block teaches that after 14 days of growth, removal of nicotinamide from media components has the most dramatic effect in reducing cell proliferation, only second to removal of dexamethasone (col. 14, lines 11-26) (see Table IV for effect of removal of nicotinamide in reduction of cell growth, e.g., 35.20 ±1.70 μg/well of DNA), clearly indicating that nicotinamide is an essential components in the culature conditions contributing to DNA proliferation. Moreover, Block teaches that proliferation of hepatocytes, in part, results from facultative stem cell growth (col. 1, lines 60-66, bridging to col. 2, and lines 1-5) **(Current claims 411, 469-471 and 478-480**). It is noted that Block describes

that expansion of cells may occur without exogenously adding nicotinamide, for example, by addition to the stock basal media of at least one supplemental component such as Dexamethasone (**Current claim 401,** in part**).**

Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made, to increase the concentration of exogenously added nicotinamide to the culture media taught by Brown R. in an attempt to provide an improved formulation of the IMDM for preferential *ex vivo* expansion (e.g. proliferation) of CD34+/CD38- hematopoietic stem cells, particularly because Block clearly discloses, in an unequivocal manner, that exposing a mixed population of hepatocytes including stem cells to nicotinamide at concentrations of 0-3050 mg/L, and preferentially 610.0 mg/L (e.g., equivalent to 5 mM), sustained long term proliferation and viability of hepatocytes. The manipulation of previously identified media components to determine cell growth and proliferation in a culture plate is within the ordinary level of skill in the art of cell and tissue culture. Because both Brown and Block teach media comprising nicotinamide for expansion of stem cells, it would have been obvious to increase exogenously added nicotinamide in the IMDM of Brown to 1.0 mM to 10 mM to achieve the predictable result of *ex vivo* expansion of hematopoietic stem cells and inhibition of differentiation of the same cell population given the results of Brown and Block demonstrating the success of the methodology and materials detailed in each of the disclosures

Response to Applicants' Arguments as they apply to rejection of claim 401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-471 and 478-480 under 35 USC § 103

At pages 6-9 of the Remarks filed on 06-29-2009, Applicants essentially argue that: 1) Brown considers nicotinamide a minor proliferative agent, and would in no way consider nicotinamide as an agent to inhibit differentiation, 2) nicotinamide concentrations of up to 10 times 4 mg/L (i.e., 0.33mM) disclosed by Brown are ineffective inhibiting the differentiation of CD34+ as evidenced by the Peled Declaration (December 30, 2008; at pages 2-4; Figure 1), 3) Brown cultures CD34+ in serum-free medium to prevent differentiation of CD34+cell and to improve CD34+ stem cell engraftment, which is in contrast to the instant invention wherein the cells require serum, nutrients, and cytokines and an effective amount of nicotinamide to inhibit differentiation, 5) Brown as a whole would readily recognize that only serum-free culture conditions and not nicotinamide are useful to inhibit CD34+ differentiation, making unobvious optimization of serum-free culture conditions, 6) Block discloses that nicotinamide is utilized as both, a proliferative agent and for its ability to maintain hepatocyte differentiation, 7) Block teaches growth of completely different cell lines, hepatocytes, and not CD34+ hematopoietic stem cells and 8) the Peled Declaration and the working example provided in the instant specification at Example 5 readily demonstrates that the present invention provides unexpected and superior properties not taught or suggested by the prior art, e.g., that the critical range l.0 mM to 10 mM exogenously added nicotinamide, inhibits differentiation of the CD34+ stem cells, while permitting expansion, *ex vivo*. **The above arguments have been fully considered but deemed unpersuasive.**

Regarding 1), 2), and 3), the fact that Brown preferentially uses a serum free medium for expansion of CD34+/CD38- for long term engrafting purposes is not disputed (p.1, [0009]). However, in preferred embodiments, Brown teaches albumin as a source of nutrients derived

from human plasma fraction (HAS) with advantages over proteins derived from animals such as bovine serum albumin (BSA) including reduced immunogenic potential. Moreover, the instant claims do not place any limitation on whether the culture conditions for expanding a CD34+ simultaneously require serum and nicotinamide. All what is required in claim 1 (b) is that "at the same time, culturing said cells under conditions which inhibit differentiations, said conditions which comprise providing nicotinamide" in an effective amount to inhibit differentiation. Thus the conditions recited in claim 401 subpart (a) are not necessarily the same as the conditions of subpart (b).

Regarding 5), Brown clearly discloses that any of the growth factors which accelerate differentiation of CD34+/CD38- cells to CD34+/CD38+ cells and thus prevent enrichment CD34+/CD38- cells should be avoided (p.6,[0068]), clearly indicating that the formulation of IMDM can be optimized for CD34+ expansion.

Regarding 6), Block clearly teaches various growth factors can be added to the stock basal media to induce accelerated growth (col. 11, lines 28-38) including concentrations of nicotinamide in the range of 1-3050 mg/L, **preferably 610.0 mg/L** (610-3050 mg/L is equivalent to 5 to 25 mM of nicotinamide), see Table II; col. 10, lines 30-50. Furthermore, removal of nicotinamide from media components has the most dramatic effect in reducing cell proliferation, as evidenced by decreased DNA synthesis in the proliferating cultures maintained in the absence of nicotinamide, e.g., 35.20 ±1.70 μg/well of DNA in relation to DNA synthesis decreased by removal of other growth factors. As the stock basal media comprises to 5 to 25 mM of nicotinamide (e.g., **610.0 mg/L to** 1-3050 mg/L), then any growth and/or differentiation of hepatocytes are implicitly anticipated by the range of nicotinamide concentration used .

Regarding 7), the fact that Block teaches proliferation of hepatocytes directly or via facultative stem cells growth, and that hepatocytes stem cells are not CD34+ hematopoietic stem cells is not disputed. However, growth of hepatocytes stem cells requires DNA proliferation. Growth of CD34+ hematopoietic stem cells requires DNA proliferation. If DNA synthesis significantly decreases in the proliferating hepatocytes cultures maintained in the absence of Nicotinamide in relation to cultures maintained in the presence of Nicotinamide at 610.0 mg/L (e.g., 5mM), removal of Nicotinamide should be reasonably expected to inhibit CD34+ hematopoietic stem cell proliferation for the same reason it prevented proliferation of hepatocytes stem cells -both hepatocyte stem cell and CD34+ hematopoietic stem cell require DNA proliferation for *ex vivo* expansion.

Regarding 8), it is noted that in the Peled Declaration at page 4, Table 1, Figure 1, nicotinamide appears to be critical for expansion of CD34+CD38- in the range of 2.5 to 5 mM after one week period, which is supported by the disclosure of Fig. 15 in the specification as filed. In contrast, concentration of nicotinamide at 1 mM is not significant in cell density of CD34+/CD38- cells, CD34+/Lin- and CD34+/(HLA-DR38)- cells in 3 weeks culture (Figures 15-17).

Claims 437 and 438 reamin rejected under 35 U.S.C. 103(a) as being unpatentable over Brown R (US Publication No. 2002/0159984, Date of Publication October 31, 2002) over Block et al., (US Patent 6,413,772, Date of Patent July 2, 2002) as applied to claims 401, 411, 412, 414, 416-419, 422-424, 462, 464-467 and 469-481 above, and further in view of Banasik et al., (1992, JBC, pp. 1569-1575, of record).

Response to Applicants' Arguments as they apply to rejection of claim 437 and 438 under 35 USC § 103

At page 9 of Remarks, Applicants allege that "Banasik does not cure the deficiencies of Brown. By contrast, Banasik merely discloses that benzamide, as well as nicotinamide, is an inhibitor of poly(ADP-ribose) synthetase activity. Banasik is silent with regard to the use of nicotinamide or nicotinamide analogs for expansion and inhibition of differentiation of hematopoietic stem cells". Such is not persuasive.

The specification defines a "nicotinamide analog" as any molecule that is known to act similarly to nicotinamide (page 18, paragraph [0270]). Banasik teaches that nicotinamide inhibits poly (ADP-ribose) synthetase activity. Moreover, Banasik discloses that benzamide inhibits poly (ADP-ribose) synthetase activity. Therefore, nicotinamide and benzamide are analogs because they inhibit the same function: ADP-ribosylation of proteins.

New Grounds of Rejection

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claim 411 and dependent claims 465 and 478-480 are rejected under 35 U.S.C. § 101 because the claimed invention is drawn to non-statutory subject matter.

Claim 411 is a product by process claim. The preamble of the claim 1 recites "A transplantable hematopoietic cell preparation comprising:...". The cells are not recited as

isolated. Thus claim 411 could broadly but reasonably interpreted as subpopulations of progenitor cells found in umbilical cord blood having the CD34+CD38- phenotype and CD34+/Lin- phenotype. Thus, the transplantable hematopoietic cell preparation encompasses a naturally-occurring cell population, which is a product of nature that is not statutory subject matter because it fails to show the "hand of man" in their construction and because they read on non-isolated mammalian cells.

35 USC § 112- First paragraph- Written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 401 and dependent claims 414, 416, 419, 422-424, 437, 438, 464 and 469-471 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to any person skilled in the art to which it pertains, or with which it is most nearly connected, at the time the application was filed, that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 401 encompasses a genus of unspecified nicotinamide derived compounds from nicotinamide or analogs of nicotinamide. Nicotinamide (NA) is a water-soluble derivative of vitamin B (e.g., amide of vitamin B3), whose physiological active forms are nicotinamide adenine dinucleotide (NAD+/NADH) and nicotinamide adenine dinucleotide phosphate

(NADP+/NADPH) (Genazzani et al., Trends in Pharmacological Sciences 1997, pp. 108-110; page 1569, col. 3, last paragraph; Fig. 2). At the time the invention was made, it was known in the art that nicotinamide is a non-competitive inhibitor of NAD (+) dependent ADP ribosyl transferase (Banasik et al., 1991, JBC; pp. 1569-1575) and inhibitor of ADP-ribosyl clyclase activity (Bruzzone et al., 2003, Biochem Journal 395-403; p. 400, col. 2). The derived nicotinamide proteins when given the broadest reasonable interpretation encompass a genus of unspecified variants of a nicotinamide in which the purine, pyridine, and ribose moieties have been modified. The specification and claims do not place any limits on the number substitutions in nicotinamide affecting its substrate binding, e.g., ADP-ribosyl clyclase and thus activity of ADP-ribosyl clyclase inhibiting differentiation of CD34+ hematopoietic stem cells while inducing expansion at concentrations of 1.0 mM to 10mM in the presence of cytokines and nutrients.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

[A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, Applicant discloses in Example 5 of the specification that *ex-vivo* expansion of stem and progenitor hematopoietic cells in the presence of a combination of 5 cytokines, SCF, TPO, FLt3, IL-6 and IL-3, with or without different concentrations of nicotinamide supplemented with 1 and 5 mM nicotinamide yielded $99x10^4$ and $180x10^4$ CD34+ cells per ml, respectively, as compared with only $35x10^4$ CD34+cells per ml in the non-treated (cytokines only) control. In addition, the re-selected CD34+ cell fraction was FACS analyzed for stem/progenitor cell markers. The results, presented in FIGS. 15-17 and 18a-b, show substantial increases in the proportion of CD34+/CD38-, CD34+/Lin- and CD34+/(HLA-DR38-) cells in cultures treated with nicotinamide (page 43; paragraph [0567]). The specification defines as "nicotinamide analog" any molecule that is known to act similarly to nicotinamide (page 18, paragraph [0270]). Moreover, the specification teaches that benzamide, nicotinethioamide, nicotinic acid and α-amino-3-indolepropionic acid are nicotinamide analogs (paragraph [108]). However, no other specifics are given about the definition of the term “analogs ” or “derivate” or how modifications of the purine, pyridine, and ribose moieties of the claimed analogs of nicotinamide inhibit differentiation of CD34+ hematopoietic stem cells while inducing expansion

at concentrations of 1.0 mM to 10mM, other than for nicotinamide.

At the time the invention was made, it was known in the art that nicotinamide is a non-competitive inhibitor of NAD (+) dependent ADP ribosyl transferase (Banasik et al., 1991, JBC; pp. 1569-1575; Colon-Otero, Blood; 1987 pp. 686-93; p. 686, col. 2) and inhibitor of ADP-ribosyl clyclase (Bruzzone et al., 2003, Biochem Journal 395-403; p. 400, col. 2). It was also known that the only enzyme in mammalian cells with homology to cyclic ADP-ribose (cADPR) has been identified as ecto-NADases/ADPRC CD38 and CD157 (Guse, 2002, Current Molecular Medicine, pp. 273-282; p. 273, col. 2, last paragraph). Moreover, it was known that purified recombinant CD38, a lymphocyte antigen, which acts as an enzyme to catalyze the synthesis of cyclic ADP-ribose (cADPR) from βNAD+, also produces NAADP using βNADP+ as a substrate in the presence of nicotinic acid (Genazzani et al., Trends in Pharmacological Sciences 1997, pp. 108-110; page 1569, col. 3, last paragraph; Fig. 2). Moreover, Genazzani et al., teaches that release from intracellular Ca2+ stores is accomplished by the small molecular compounds cADPR and NAADP. Additionally, Podesta et al., (the *FASEB* Journal 2000, pp. 680-690) teaches that cADPR increases intracellular free calcium and stimulates proliferation of human hematopoietic progenitors. Munshi et al., discloses that nicotinamide inhibits expression of CD38, a multifunctional enzyme (Munshi et al., J Biol Chem. 2002 pp. 49453-8) in human HL-60 (human promyelocytic leukemia cell line) . Likewise, Bruzzone et al., (2003, Biochem Journal 395-403) discloses that nicotinamide at concentrations of 10mM inhibits the activity of cADPR activity in PBMN (p. 400, col. 2, last paragraph). However, the art is silent on other analogs or derivatives of nicotinamide exhibiting inhibition of ADP-ribosyl clyclase activity. The skilled artisan understands that one nucleotide change in a DNA molecule or one amino acid

change in the polypeptide encoded by the DNA molecule could result in the loss of its biological activity as demonstrated in the generation of sickle-cell anemia wherein on specific amino acid mutation gave rise to the inherited disease (Biochemistry, John Wiley and Sons, 1990, p. 126-129). Even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (Ngo et al, 1994). Thus the ability to determine *a priori* whether a mutation in a region critical to the claimed peptide structure/function relationship, particularly, various sites or regions directly involved in binding of nicotinamide analogs to its ADP-ribosyl clyclase substrate so as inhibit differentiation of CD34+ hematopoietic stem cells while inducing expansion at concentrations of 1.0 mM to 10mM in the presence of cytokines and nutrients is not predictable. The specification does not disclose what purine, pyridine, and ribose moieties have been modified in nicotinamide nor concentration of any analog effective to retain full or even partial activity when substrate binding**.** This may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site for the ADP-ribosyl clyclase has to be recognized by the cognate nicotinamide which must have the proper three-dimensional configuration to effectively interact with its substrate. There is no structure/function relationship taught at all for claimed genus of unspecified nicotinamide derivatives or analogs of nicotinamide other than for nicotinamide. This disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims, as one of skill in the art cannot envision all the modified forms derived from nicotinamide based on the teachings in the specification. This limited information is not deemed sufficient to reasonably

convey to one skilled in the art that Applicant is in possession of the claimed genus of nicotinamide analogs or nicotinamide derivatives inhibiting differentiation of CD34+ hematopoietic stem cells while inducing expansion at concentrations of 1.0 mM to 10mM in the presence of cytokines and nutrients at the time the invention was made.

Conclusion

Claims 401, 411, 414, 416, 419, 422-424, 437, 438, 464, 465, 469-471 and 478-480 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Maria Leavitt/

Maria Leavitt
Primary Examiner, Art Unit 1633